

REC'D 26 OCT 2001

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference R1562-PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/BE00/00066	International filing date (day/month/year) 19/06/2000	Priority date (day/month/year) 17/06/1999
International Patent Classification (IPC) or national classification and IPC C07K1/00		
Applicant UNIVERSITEIT GENT et al.		


1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 10/01/2001	Date of completion of this report 25.10.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Masturzo, P Telephone No. +31 70 340 2275



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/BE00/00066

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*
Description, pages:

1-52 as originally filed

Claims, No.:

1-35 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/BE00/00066

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-35.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-35 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes: Claims

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/BE00/00066

	No:	Claims	1-35
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-35
Industrial applicability (IA)	Yes:	Claims	1-35
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-35 were not searched in their entirety. In fact the wording of these claims abounded in unclear, vague and undefined expressions that a complete search was not deemed to be possible. What was searched were the real examples provided in the text (polymers of N-(2-hydroxyethyl)-glutamine, N-(2-hydroxypropyl)-glutamine and N-(2-dihydroxypropyl)-glutamine) and pertinent methods for their preparation, their conjugates and their use for the modification of biologically active materials. Despite the statement issued with the Search Report, also claims 28-35 were searched only insofar as limited to the above subject.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO-A-9819710 (Schacht et al.);
D2: WO-A-9736616 (University of Birmingham);
D3: CA 118: 45611 (1992).

1) D2 (see throughout) discloses the preparation of polymers of N-(2-hydroxyethyl)-glutamine and their use for a pertinent purpose. Another example of the preparation of these polymers and of their use for pertinent purposes is provided by D3. Therefore claims 1-35 as further defined under the previous heading, are objected to under Art. 33(2) PCT because they are not new.

2) In the light of the (partially overlapping) documents D2 and D3, as well as of the general disclosure D1 (from the same applicant) the problem underlying the present application is set as to provide alternative polymers for the modification of biologically active materials. This scope is reached by the polymers of N-(2-hydroxypropyl)-glutamine and N-(2-dihydroxypropyl)-glutamine), which were previously undisclosed

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/BE00/00066

and have been demonstrated to have been prepared and also to have been used for a pertinent scope. However, these compounds, whose formula can be formulated very easily starting from polymers of the N-(2-hydroxyethyl)-glutamine, are prima facie obvious and therefore not inventive under Art. 33(3) PCT.

3) Claims 1-35 are endowed with industrial applicability under Art. 33(4) PCT.

Re Item VIII

Certain observations on the international application

Claims 1-35 are objected to under Art. 6 and Rule 6 PCT, as they contain many unclear and vague expressions; moreover, the use made by the applicant of the term "example" in the description makes completely unclear which are the real compounds prepared to embody the present application, which are the intermediate ones etc.

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/BE 00/00066

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08G69/10 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C08G A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 19710 A (SCHACHT ET AL.) 14 May 1998 (1998-05-14) example 7	1-35
A	WO 97 36616 A (SEYMOUR ET AL.) 9 October 1997 (1997-10-09) page 2 -page 5	1-35
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document member of the same patent family

Date of the actual completion of the international search

29 May 2001

Date of mailing of the international search report

13/06/2001

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Masturzo, P

INTERNATIONAL SEARCH REPORT

Int. l. Application No
PCT/BE 00/00066

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; DE MARRE, ANNE ET AL: "Preparation of 4-nitrophenyl carbonate esters of poly'5N-(2-hydroxyethyl) L-glutamine! and coupling with bioactive agents" retrieved from STN Database accession no. 118:45611 CA XP002168431 & MAKROMOL. CHEM. (1992), 193(12), 3023-30 , ' 1992, abstract</p> <p>----</p>	1-35
A	<p>GB 781 202 A (F J WEYMOUTH) 14 August 1957 (1957-08-14) the whole document</p> <p>----</p>	1-35
A	<p>K E GONSALVES & P M MUNGARA: "Synthesis and properties of degradable polyamides and related polymers " TRENDS IN POLYMER SCIENCE., vol. 4, no. 1, January 1996 (1996-01), pages 25-31, XP004049307 ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM., NL ISSN: 0966-4793 the whole document</p> <p>-----</p>	1-35

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

Claims Nos.: 1-27

Present claims 1-27 relate to an extremely large number of possible compounds and related methods. In fact, the claims contain so many options and variables that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely claims 1-27 as further limited to the polymers of the poly-'N-(2-hydroxyethyl)-glutamine!', poly-'N-(2-hydroxypropyl)-glutamine!' and poly-'N-(2-dihydroxypropyl)-glutamine!' as in the only provided examples, as well as to the methods for their preparation, to their conjugates and their use.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. l. Application No

PCT/BE 00/00066

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9819710 A	14-05-1998	AU 4873997 A EP 0941123 A	29-05-1998 15-09-1999
WO 9736616 A	09-10-1997	EP 0891191 A	20-01-1999
GB 781202 A	14-08-1957	NONE	

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 15 February 2001 (15.02.01)	
International application No. PCT/BE00/00066	Applicant's or agent's file reference R1562-PCT
International filing date (day/month/year) 19 June 2000 (19.06.00)	Priority date (day/month/year) 17 June 1999 (17.06.99)
Applicant SCHACHT, Etienne, Honoré et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

10 January 2001 (10.01.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Juan Cruz Telephone No.: (41-22) 338.83.38
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(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 December 2000 (28.12.2000)

PCT

(10) International Publication Number
WO 00/78791 A2

(51) International Patent Classification⁷: C07K 1/00

(21) International Application Number: PCT/BE00/00066

(22) International Filing Date: 19 June 2000 (19.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99870125.4 17 June 1999 (17.06.1999) EP

(71) Applicant (for all designated States except US): UNIVERSITEIT GENT [BE/BE]; St. Pietersnieuwstraat 25, B-9000 Gent (BE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): SCHACHT, Etienne, Honoré [BE/BE]; Rysseveldstraat 99, B-8840 Staden (BE). TONCHEVA, Veska [BG/BE]; Pacificatielaan 5, B-9000 Gent (BE).

(74) Agents: BIRD, William et al.; Bird Goën & Co., Vilvoordsebaan 92, B-3020 Winksele (BE).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

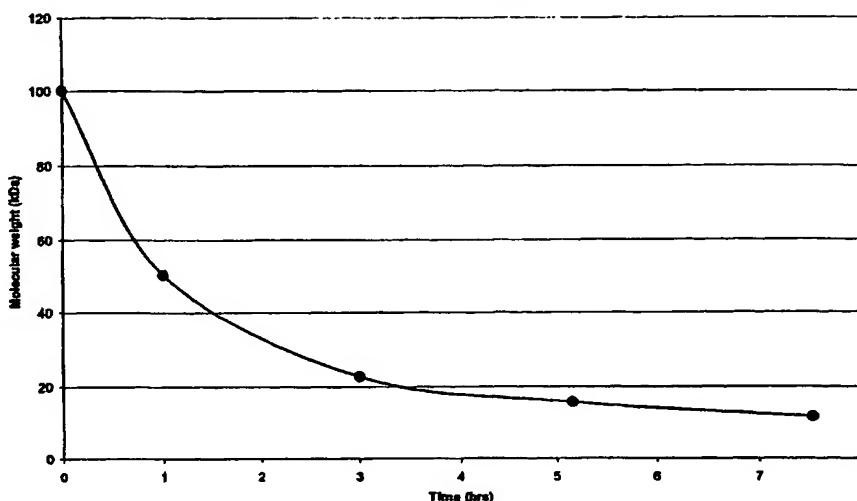
Published:

— Without international search report and to be republished upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: FUNCTIONAL POLY- α -AMINOACID DERIVATIVES USEFUL FOR THE MODIFICATION OF BIOLOGICALLY ACTIVE MATERIALS AND THEIR APPLICATION

Enzymatic degradation of PHEG



(57) Abstract: A linear poly- α -amino-acid derivative has at least glutamic or aspartic or serinic repeating units and additionally having a functional group at one or both ends of the polymer backbone and/or only a single functional group as a side group on the polymer backbone, the said functional end group and/or side group being other than alcohol. The said functional derivative is useful for the modification of biologically active materials.

WO 00/78791 A2

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference R1562-PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/BE 00/ 00066	International filing date (<i>day/month/year</i>) 19/06/2000	(Earliest) Priority Date (<i>day/month/year</i>) 17/06/1999
Applicant UNIVERSITEIT GENT		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-27

Present claims 1-27 relate to an extremely large number of possible compounds and related methods. In fact, the claims contain so many options and variables that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely claims 1-27 as further limited to the polymers of the poly-'N-(2-hydroxyethyl)-glutamine!', poly-'N-(2-hydroxypropyl)-glutamine!' and poly-'N-(2-dihydroxypropyl)-glutamine!' as in the only provided examples, as well as to the methods for their preparation, to their conjugates and their use.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/BE 00/00066

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C08G69/10 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C08G A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

29 May 2001

Date of mailing of the international search report

13/06/2001

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Masturzo, P

INTERNATIONAL SEARCH REPORT

International Application No

PCT/BE 00/00066

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; DE MARRE, ANNE ET AL: "Preparation of 4-nitrophenyl carbonate esters of poly'5N-(2-hydroxyethyl) L-glutamine! and coupling with bioactive agents" retrieved from STN Database accession no. 118:45611 CA XP002168431 & MAKROMOL. CHEM. (1992), 193(12), 3023-30 , 1992, abstract ---	1-35
A	GB 781 202 A (F J WEYMOUTH) 14 August 1957 (1957-08-14) the whole document ---	1-35
A	K E GONSALVES & P M MUNGARA: "Synthesis and properties of degradable polyamides and related polymers " TRENDS IN POLYMER SCIENCE., vol. 4, no. 1, January 1996 (1996-01), pages 25-31, XP004049307 ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM., NL ISSN: 0966-4793 the whole document -----	1-35

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/BE 00/00066

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9819710	A	14-05-1998	AU	4873997 A	29-05-1998
			EP	0941123 A	15-09-1999
WO 9736616	A	09-10-1997	EP	0891191 A	20-01-1999
GB 781202	A	14-08-1957	NONE		

PCT



WIPO

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

10/009808

Applicant's or agent's file reference R1562-PCT		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/BE00/00066	International filing date (day/month/year) 19/06/2000	Priority date (day/month/year) 17/06/1999	
International Patent Classification (IPC) or national classification and IPC C07K1/00		RECEIVED SEP 25 2002 TECH CENTER 1600/2900	
Applicant UNIVERSITEIT GENT et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 10 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none">I <input checked="" type="checkbox"/> Basis of the reportII <input type="checkbox"/> PriorityIII <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicabilityIV <input type="checkbox"/> Lack of unity of inventionV <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statementVI <input type="checkbox"/> Certain documents citedVII <input type="checkbox"/> Certain defects in the international applicationVIII <input checked="" type="checkbox"/> Certain observations on the international application			
Date of submission of the demand 10/01/2001		Date of completion of this report 19.12.2001	
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016		Authorized officer Masturzo, P Telephone No. +31 70 340 2275 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/BE00/00066

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
Description, pages:

1-52 as originally filed

Claims, No.:

1-36 as received on 06/12/2001 with letter of 26/11/2001

Drawings, sheets:

1/2,2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:

**INTERNATIONAL PRÉLIMINARY
EXAMINATION REPORT**

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☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-36

Inventive step (IS)	Yes: Claims	
	No: Claims	1-36

Industrial applicability (IA)	Yes: Claims	1-36
	No: Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

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Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-36 were now searched in their entirety.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO-A-9819710 (Schacht et al.);
D2: WO-A-9736616 (University of Birmingham);
D3: CA 118: 45611 (1992).

1) D2 (see throughout) discloses the preparation of polymers of N-(2-hydroxyethyl)-glutamine and their use for a pertinent purpose. Another example of the preparation of these polymers and of their use for pertinent purposes is provided by D3. Therefore claims 1-36 are objected to under Art. 33(2) PCT because they are not new. In fact all polymers of amino acids which are not specifically modified exhibit a free carboxy and a free amino group; those groups are reactive and situated at the extremities of the molecule.

2) In the light of the (partially overlapping) documents D2 and D3, as well as of the general disclosure D1 (from the same applicant) the problem underlying the present application is set as to provide alternative polymers for the modification of biologically active materials. This scope is reached by the some polymers of the present application which are therefore inventive under Art. 33(3) PCT. However, this cannot be extended to the ensemble of the claims, which have been objected to in the previous heading.

3) Claims 1-36 are endowed with industrial applicability under Art. 33(4) PCT.

Re Item VIII

Certain observations on the international application

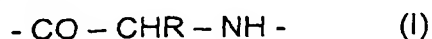
**INTERNATIONAL PRELIMINARY
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Claims 1-36 are objected to under Art. 6 and Rule 6 PCT. In fact there are only examples of different modified poly-glutamine, whereas all polymers, also including non-amino-acid component, might fall under claim 1ff. and this makes most of the present application devoid of support.

28. 11. 2001

1. A linear monofunctional or multifunctional poly- α -amino-acid derivative⁹⁵ having at least glutamic or aspartic or serinic repeating units in the polymer backbone, the said glutamic or aspartic or serinic repeating units having the formula:



wherein:

- R is defined as $-(CH_2)_n-CO-OR_1$ or $-(CH_2)_n-CO-NHR_2$ or CH_2OH ,

- n is 1 or 2,

- R_1 is selected from hydrogen, C_{1-20} alkyl, polyhalo C_{1-6} alkyl, aryl C_{1-6} alkyl and heteroaryl C_{1-6} alkyl, and

- R_2 is C_{1-6} alkyl substituted with at least one alcohol group, characterized in additionally having a functional group at one or both ends of the polymer backbone, the said functional end group(s) being selected from amine, carboxyl, ester, carbonate, thiol, thiol precursor, thioisocyanate, thiocarbonate, urea, thiourea, aldehyde, acetal, N-carboxyanhydride, oxycarbonyl, maleimide or any vinyl group suitable for radical, anionic or cationic polymerization.

2. A linear multifunctional poly- α -amino-acid derivative according to claim 1, having a functional group at both ends of the polymer backbone, characterized in additionally having a single functional group as a side group.

3. A linear poly- α -amino-acid derivative according to claim 2, wherein the said functional side group is selected from the group consisting of amine, thiol precursor, thioisocyanate, thiocarbonate, urea, thiourea, acetal, N-carboxyanhydride, oxycarbonyl, maleimide and any vinyl group suitable for radical, anionic or cationic polymerization.

4. A linear multifunctional poly- α -amino-acid derivative according to claim 2, wherein the said functional side group is selected from carboxyl,

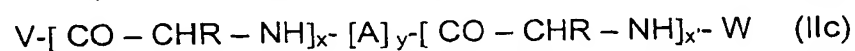
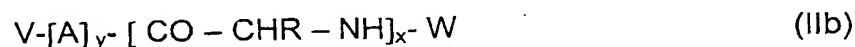
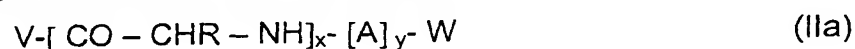
ester, carbonate, thiol and aldehyde.

5. A linear poly- α -amino-acid derivative according to any of claims 1 to 4, additionally comprising repeating units of one or more comonomer(s) copolymerizable with the α -amino-acid sequence containing glutamic or aspartic or serinic repeating units.

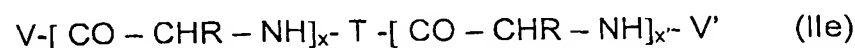
6. A linear poly- α -amino-acid derivative according to claim 5, wherein the said co-monomer is any naturally occurring α -amino-acid other than glutamic acid, aspartic acid and serine.

7. A linear poly- α -amino-acid derivative according to claim 5, wherein the said co-monomer is a polymer block or sequence derived from ethylene oxide or propylene oxide or mixtures thereof or from a polyhydroxyalkanoate.

8. A linear poly- α -amino-acid derivative according to any of claims 1 to 7, being multifunctional and having any of the following formulae:



W



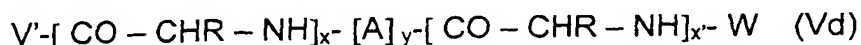
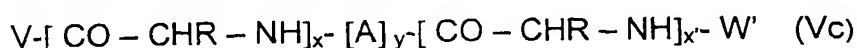
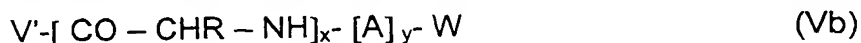
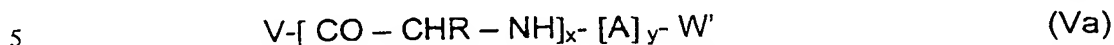
W

wherein:

- R is as defined in claim 1,
- x or, where applicable, x + x' range from 2 to 2,000,
- each of V and W independently represent a functional group,
- A is at least a co-monomer copolymerizable with the α -amino-acid sequence containing glutamic or aspartic or serinic repeating units,
- y ranges from 0 to 500,
- T is a spacing unit selected from lysine and ornithine, and

- V' is a non-reactive end group.

9. A linear poly- α -amino-acid derivative according to any of claims 1 to 7, being monofunctional and having any of the following formulae:



W

wherein:

- R is as defined in claim 1,
 - x or, where applicable, x + x' range from 2 to 2,000, and
 - each of V and W independently represent a functional group,
 15 - A is at least a co-monomer copolymerizable with the α -amino-acid sequence containing glutamic or aspartic or serinic repeating units,
 - y ranges from 0 to 500,
 - T is a spacing unit selected from lysine and ornithine, and
 - V' and W' are non-reactive end groups.

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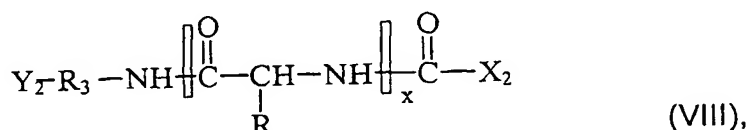
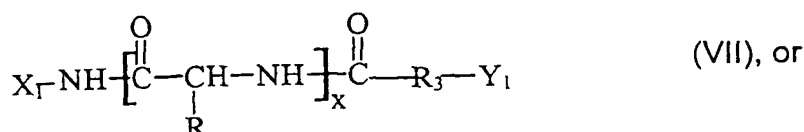
10. A linear poly- α -amino-acid derivative according to claim 8 or claim 9, wherein A is represented by the formula $-CO-CHR'-NH-$ (III), wherein R' is the side-chain group of an α -amino acid other than glutamic acid or aspartic acid or serine, or by the formula



- R'' is selected from hydrogen and methyl, and
 - X' is selected from a single bond and oxygen,
 or A is a repeating unit derived from a hydroxyalkanoate.

- 30 11. A linear poly- α -amino-acid derivative according to any of claims 8 to 10, wherein each of V' and/or W' is selected from C₁₋₂₀ alkyl, aryl, amide, oxyC₁₋₂₀alkyl, arylC₁₋₂₀alkyl, heteroaryl and heteroarylC₁₋₂₀alkyl.

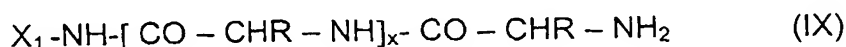
12. A linear poly- α -amino-acid derivative according to claim 1, having at least one protective end group and being represented by the following formulae:



wherein:

- R is $-(CH_2)_n-CO-NHR_2$,
- R_2 and n are as defined in claim 1,
- x ranges from 2 to 2,000,
- X_1 is $-R_4-Z_1-A_1$,
- each of R_3 and R_4 is independently selected from $(CH_2)_m$, arylene, C_{1-6} alkylarylene and aryl C_{1-6} alkylene,
- m is from 2 to 20,
- Y_1 is $-Z_2-A_2$,
- X_2 is $-R_4-Z_3-A_3$ or $-O-R_4-Z_3-A_3$,
- Y_2 is $-Z_4-A_4$,
- each of Z_1 , Z_2 , Z_3 and Z_4 is independently selected from NH, O, S, C(O)O, C(S)O, CO, CS, $-OCH-O-$ and $C=N-R_5$,
- each of A_1 , A_2 , A_3 and A_4 is a protective group suitable for Z_1 , Z_2 , Z_3 and Z_4 respectively, and
- R_5 is selected from hydrogen, C_{1-6} alkyl, aryl and C_{1-6} alkylaryl, heteroaryl and C_{1-6} alkylheteroaryl.

13. A linear poly- α -amino-acid derivative according to claim 1, being represented by the formula:



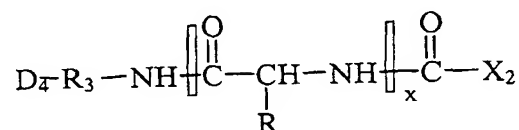
wherein:

- X_1 is $-R_4-Z_1-A_1$,
- R_4 is selected from $(CH_2)_m$, arylene, C_{1-6} alkylarylene and aryl C_{1-6}

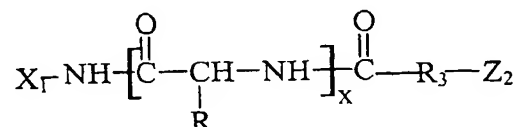
alkylene,

- x ranges from 2 to 2,000,
- R is defined as $-(CH_2)_n-CO-OR_1$,
- R_1 and n are as defined in claim 1,
- Z_1 is selected from NH, O, S, C(O)O, C(S)O, CO, CS, -OCH-O- and
C = N - R_5 ,
- A_1 is a protective group suitable for Z_1 , and
- R_5 is selected from hydrogen, C_{1-6} alkyl, aryl and C_{1-6} alkylaryl,
heteroaryl and C_{1-6} alkylheteroaryl.

14. A linear poly- α -amino-acid derivative according to claim 1, being represented by any of the respective formulae:



(X), and



(XI), wherein:

- R is $-(CH_2)_n-CO-NHR_2$,
- R_2 and n are as defined in claim 1,
- x ranges from 2 to 2,000;
- X_1 is $-R_4-Z_1-D_1$,
- each of R_3 and R_4 is independently selected from $(CH_2)_m$, arylene,
 C_{1-6} alkylarylene and aryl C_{1-6} alkylene,
- m is from 2 to 20,
- each of R_3-Y_1 and R_3-Y_2 may be a group including a vinyl
terminal moiety,
- X_2 is $-R_4-Z_3-D_3$,
- each of Z_1 , Z_2 , Z_3 and Z_4 is independently selected from NH, O, S,
C(O)O, C(S)O, CO, CS, -OCH-O- and C = N - R_5 ,

- each of D_1 , D_2 , D_3 and D_4 is independently selected from hydrogen, aryl, heteroaryl, succinimidyl, vinyl, C_{1-6} alkylcarbonyl,
- each of $Z_1 - D_1$, $Z_2 - D_2$, $Z_3 - D_3$ and $Z_4 - D_4$ may be independently selected from maleimidyl, disulfide, α -haloacetoxy and C_{1-6} alkyloxy-methylsulfide, and
- R_5 is selected from hydrogen, C_{1-6} alkyl, aryl and C_{1-6} alkylaryl, heteroaryl and C_{1-6} alkylheteroaryl.

15. A linear poly- α -amino-acid derivative according to claim 14, wherein D_1 is different from D_2 and D_3 is different from D_4 .

16. A process for making a linear poly- α -amino-acid derivative according to any of claims 1 to 15, including a step comprising polymerizing a monomer or mixture of monomers comprising at least the N-carboxy anhydride of an amino-acid selected from glutamic acid, aspartic acid, serine and oxygen-protected serine in the presence of an effective amount of a multifunctional initiator containing at least one primary amino group and further containing at least another functional group selected from maleimide, thioisocyanate, thiocarbonate, urea, thiourea, aldehyde, acetal, oxycarbonyl, vinyl, ester, carbonate, thiol precursor, protected amine and protected carboxylic acid and/or in the presence of an effective amount of a bi-functional terminating reagent.

17. A process according to claim 16, wherein the multifunctional initiator is selected from amino-acid esters, α -amino- ω -di- C_{1-6} alkylacetals, α, α' -diamino C_{1-6} alkyldisulfides and α -amino- ω -maleimido alkanoic acid amides.

18. A process according to claim 16 or claim 17, wherein the amount of the multifunctional initiator ranges between 0.2 and 30 mole % with respect to the N-carboxy-anhydride monomer.

19. A process according to any of claims 16 to 18, wherein the amount of

the bi-functional terminating reagent ranges between 2 and 5 equivalents with respect to the molar amount of the multifunctional initiator.

- 5 20. A process according to any of claims 16 to 19, further including aminolysis of the pending R_1 group of the glutamic, aspartic or serinic repeating unit derived from glutamic acid, aspartic acid or serine by means of an effective amount of an amino-alcohol, in the presence of an effective amount of a reaction promoter.
- 10 21. A process according to claim 20, wherein the effective amount of the amino-alcohol used during the said aminolysis step ranges from 1 to 50, equivalents with respect to the monomeric units in the polymer.
- 15 22. A process according to claim 20 or claim 21, wherein the effective amount of the reaction promoter ranges from 0.5 to 5 equivalents with respect to the monomeric units in the polymer.
- 20 23. A process for making a linear poly- α -amino-acid derivative according to any of claims 1 to 15, including:
- a first step of N-acylating part of an α -amino-acid selected from glutamic acid, aspartic acid and serine, then separately treating the N-acylated α -amino-acid and the remaining part of the said α -amino-acid in order to form a mixture of the corresponding N-carboxy anhydrides, and
 - 25 - a second step of copolymerizing the said mixture of N-carboxy anhydrides in the presence of an initiator.
- 30 24. A process according to claim 23, wherein the N-carboxy anhydride of the α -amino-acid is used in excess of the N-carboxy anhydride of the N-acylated α -amino-acid.
25. A process according to claim 23 or claim 24, wherein the N-carboxy

anhydride-terminated polymer obtained in the second step is reacted with a reagent having the formula $H_2N - R_3 - Y_2$, wherein:

- R_3 is selected from $(CH_2)_m$, arylene, C_{1-6} alkylarylene and aryl C_{1-6} alkylene,
- Y_2 is $-Z_4 - A_4$,
- Z_4 is selected from NH, O, S, C(O)O, C(S)O, CO, CS, -OCH-O- and $C = N - R_5$,
- A_4 is a protective group suitable for Z_4 , and
- R_5 is selected from hydrogen, C_{1-6} alkyl, aryl and C_{1-6} alkylaryl, heteroaryl and C_{1-6} alkylheteroaryl.

26. A biodegradable article containing a copolymer comprising at least a moiety derived from a poly- α -amino-acid derivative according to any of claims 1 to 15, provided that the functional group at one or both ends thereof is an unsaturated group.

27. Use of a poly- α -amino-acid derivative according to any of claims 1 to 15 for the modification of a biologically-active ingredient.

28. An enzymatically degradable poly- α -amino-acid derivative according to any of claims 1 to 15, containing a L-amino-acid sequence.

29. The product of coupling a poly- α -amino-acid derivative according to any of claims 1 to 15 with a biomolecule.

30. The product of claim 29, wherein the said biomolecule is a therapeutic agent, prophylactic agent, diagnostic agent, protein, peptide, hormone, antibody or fragment thereof, oligonucleotide, plasmid, DNA, interleukin, interferon, enzyme or fragment thereof.

31. The product of claim 29 or claim 30, being an antibody modified by means of the said functional poly- α -aminoacid derivatives and having a second functionality for hooking and/or being able to attach

another targeting group such as an antibody, a peptide, an oligopeptide or a saccharide.

- 5 32. Use of a non degradable poly- α -amino-acid derivative according to any of claims 1 to 15, containing a D-amino-acid sequence, for the surface modification of a biomaterial.
- 10 33. A synthetic polymer for a polymer-based carrier vehicle or vector for delivery of DNA or other nucleic acid material to target cells in a biological system, comprising a linear poly- α -amino-acid derivative according to any of claims 1 to 15.
- 15 34. A synthetic polymer for a polymer-based carrier vehicle or vector according to claim 33, further comprising a synthetic vector component such as polyethyleneimine, poly-L-lysine, a star-shaped dendrimer or chitosan.
- 20 35. A method of treatment of a patient in need of such treatment, comprising administration to said patient of a biologically-active ingredient modified by or a nucleic acid material carried by a polymer system comprising a linear poly- α -amino-acid derivative according to any of claims 1 to 15.
- 25 36. A linear monofunctional or multifunctional poly- α -amino-acid derivative having at least glutamic or aspartic or serinic repeating units in the polymer backbone, the said glutamic or aspartic or serinic repeating units having the formula:
- $$\text{- CO - CHR - NH -} \quad (I)$$
- wherein:
- 30 - R is defined as $\text{-(CH}_2)_n\text{- CO - OR}_1$ or $\text{-(CH}_2)_n\text{- CO - NHR}_2$ or CH_2OH ,
- n is 1 or 2,
- R_1 is selected from hydrogen, C_{1-20} alkyl, polyhalo C_{1-6} alkyl, aryl C_{1-6}

alkyl and heteroarylC₁₋₆ alkyl, and

- R₂ is C₁₋₆ alkyl substituted with at least one alcohol group, characterized in additionally having a functional group at one or both ends of the polymer backbone, the said functional end group(s) being other than alcohol.

5

PATENT COOPERATION TREATY

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REC'D 24 DEC 2001
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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

The International Bureau of WIPO
34, chemin des Colombettes
CH - 1211 Geneva 20
Switzerland

PCT

NOTIFICATION CONCERNING
DOCUMENTS TRANSMITTED

Date of mailing
(day/month/year)

19.12.2001

International application No: PCT/BE00/00066

This International Preliminary Examining Authority transmits herewith the following documents:

1. ☐ demand (Rule 61.1(a)).
2. ☒ copy of the international preliminary examination report and its annexes (Rule 71.1).
3. ☐ _____ other documents (*specify*):

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